REMARKS

Entry of the Amendment and reconsideration of the claims is respectfully requested.

Claims 32, 35, 41, 43, 44, 57 and 71-73 have been amended. Claim 35 has been amended to comply with the new revised amendment format. Claim 41 and 43 have been amended to reflect their dependency on claim 32. Claim 44 has been amended to further clarify the invention. Previously misnumbered claims 69-71 have been renumbered 71-73 in accordance with 37 CFR 1.126. Support for the amendments to the claims is found throughout the specification as originally filed, including at page 20, line 30 to page 21, line 3. No new matter has been introduced with the foregoing amendments.

After entry of the amendment, claims 32, 35, 38, 39, 41-44, 46, 48, 49, and 51-73 will be pending. Claims 56, 58-61, 64, and 66-70 have been withdrawn by the Examiner.

Restriction Requirement

Pursuant to the provisional election made during a telephone conversation with the Examiner on 10/7/2004, Applicants elect, without traverse, the single probe sequence hybridizing to SEQ ID NO:1, nucleotides 265-288, claims 57, 62, 63, 65 and 69-73.

Indefiniteness

Claims 41-43, 44, 46, 48-49, 51-53, 65 and 71-73 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

According to the Office Action, claims 41-43 and 72 lack clarity as they depend from claim 40, which has been canceled. Claim 41 has been amended to reflect its dependency on claim 32 instead of canceled claim 40. Withdrawal of the rejection under 35 U.S.C. § §112, second paragraph, is respectfully requested.

The Office Action alleges the detecting step in claims 44, 46, 48-49, 51-53, 65, and 71-73 lacks clarity. Applicants amended the claims to more particularly recite the detecting step and clarify the significance of the hybridization signal. The amendment clarifies that detecting a hybridization signal indicates hybridization between the nucleic acid probe and a variant CGI-69

polynucleotide in the sample. Withdrawal of the rejection under 35 U.S.C. §112, second paragraph, is respectfully requested.

Enablement

Claims 32, 35, 38, 39, 41-44, 46, 48-49, and 51-73 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Office Action alleges there is no evidence of correlating CGI-69 and variants thereof to metabolic disorders or other biological function, and given that lack of correlation there is no utility in one of skill in the art practicing the claimed invention (*see*, pages 8-9 of the Office Action). Applicants respectfully disagree.

Applicants contend that one of skill in the art reading the specification would be able to practice a method of detecting a variant CGI-69 polynucleotide without undue experimentation. There are many factors to be considered in the analysis of enablement, including breath of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation. MPEP 2164.01(a) citing *In Re Wands*, 858 F.2d 731, 737 (7th Cir. 1988). Only a reasonable correlation between the disclosure and the claimed subject matter is required.

Applicants' claims are directed to methods of identifying variant CGI-69 polynucleotides from a biological sample. Applicants demonstrated that human CGI-69 has 86% amino acid sequence identity with murine CGI-69. Murine CGI-69 was found to be upregulated 2 fold in BAT in cold-challenged mice, indicating a role in BAT thermogenesis. Analysis of the human CGI-69 protein structure indicated the presence of 4 mitochondrial carrier domains, 6 potential transmembrane spanning domains, a likely mitochondrial localization, and 3 regions with reasonable homologies to putative mitochondrial energy transfer signature sequence in known UCP homologs. Mitochondrial localization was confirmed using labeled CGI-69. Based on the mitochondrial localization and the significant amino acid sequence identity and structural similarities to mouse CGI-69, Applicants submit one skilled in the art would understand that a CGI-69 variant has the function of a mitochondrial carrier protein.

The specification provides considerable direction and guidance on how to practice the claimed invention, including working examples. Applicants provided several examples of variant CGI-69 polynucleotides and the nucleic acid sequences of the probes used to identify the polynucleotides. The claimed methods are useful for identifying cells that express CGI-69 polypeptides and assessing, measuring or quantitating cellular respiration in these cells, as taught for example in Example 3. In view of the disclosure, one skilled in the art would have been able to use the claimed methods to identify variant CGI-69 polynucleotides from a biological sample without undue experimentation. Applicants submit this use is sufficient to meet the enablement requirement.

Applicants have asserted several utilities for the claimed methods of detecting the variant polynucleotides including detecting mutations and polymorphisms that relate to disease, disease progression or response to therapy. See the specification at page 8. Using the mouse sequence several isoforms of the polypeptides were identified. See the specification at page 85, lines 7-15. Applicants have also described the use of a method of detecting the polypeptides to monitor metabolic conditions in the presence or absence of treatment. See the specification at page 8, lines 24-28. Applicants submit that upregulation of a polynucleotide encoding a polypeptide comprising SEQ ID NO:3 indicates that it is useful as a marker of increased metabolism.

Applicants submit that only a reasonable correlation between the claimed method and the utility of the method is required. Moreover, the fact that CGI-69 and/or isoforms thereof may not function as a mitochondrial uncoupling protein does not prevent the claimed methods being useful for monitering metabolism. The significant induction in BAT of cold challenged mice indicates that CGI-69 and variants thereof are associated with an increase in metabolism.

Based on the foregoing, Applicants submit one of skill in the art would have been able to use the claimed methods without undue experimentation. The level of skill in the art is high and the specification provides considerable direction and guidance on how to practice the claimed invention, including working examples. Accordingly, withdrawal of the enablement rejection is respectfully requested.

Written Description

Claims 32, 35, 38, 39, 41-44, 46, 48-49 and 51-73 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner alleges the specification provides insufficient written description to support the genus encompassed by the claims. Applicants respectfully traverse the rejection.

Applicants' claims are directed to methods for identifying a polynucleotide encoding a polypeptide comprising an amino acid sequence having at least 98% sequence identity to SEQ ID NO:3, wherein the variant polynucleotide encodes an allelic variant of the polypeptide comprising an amino acid sequence of SEQ ID NO:3. The specification as filed provides ample written description for the claimed methods. Based on the information provided in the specification, one skilled in the art would be able to carry out the claimed methods to detect a polynucleotide encoding a polypeptide comprising an amino acid sequence having at least 98% sequence identity to SEQ ID NO:3. The level of skill in the art is high. One skilled in the art would be familiar with commonly used procedures to design probes and primers for hybridization purposes. The specification also teaches a number of probes and primers that are useful for identifying human CGI-69, human CGI_L-69, or mouse CGI-69 (*see*, page 84, line 19 to page 85, line 3 of the specification).

Using the methods described in Example 2, for example, Applicants identified a novel splice variant of human CGI-69 (CGI_L-69) and isolated a variety of CGI-69 clones using the designated primers and probes (*see*, page 85, lines 7-22 of the specification). Moreover, several of these clones were isoforms or allelic variants having amino acid substitutions and insertions. See the specification at page 85, lines 7-15. At least 3 different isoforms were identified. Applicants submit that the identification of these different isoforms is sufficient to support the genus as claimed. Comparison of the amino acid and nucleic acid sequences of CGI-69 and CGI_L-69 revealed that CGI_L-69 may be distinguished from CGI-69 by an amino acid sequence corresponding to amino acid residues 65 to 72 of SEQ ID NO:3 or a nucleic acid sequence corresponding to nucleotides 263 to 286 of SEQ ID NO:1.

Based on the foregoing, Applicants submit one of skill in the art would have envisioned the procedures for identifying a polynucleotide encoding a polypeptide

comprising an amino acid sequence having at least 98% sequence identity to SEQ ID NO:3. Withdrawal of the written description rejection is respectfully requested.

New Matter

Claims 57 and 65 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new subject matter. Applicants respectfully traverse the rejection.

The Office Action alleges the phrase "nucleotides 265 to 288 of SEQ ID NO:1" in claims 57 and 65 is new matter. The claims as amended recite nucleotides 263 to 286 of SEQ ID NO:1. Example 2 describes isolation of CGI-69$_L$ (SEQ ID NO:3), a novel splice variant of CGI-69 containing an 8 amino acid insert. Alignment of the nucleotide sequence of CGI-69$_L$ (SEQ ID NO:1) and CGI-69 (SEQ ID NO:2) reveals a 24 nucleotide insert (nucleotides 263-286) in SEQ ID NO:1 encoding the 8 amino acids. The CGI-69$_L$ probe (SEQ ID NO:12) used in Example 2 hybridized to a portion of the 24 nucleotide insert in SEQ ID NO:1.

In view of the forgoing, Applicants submit the phrase "nucleotides 263 to 286 of SEQ ID NO:1" has sufficient basis in the specification and does not constitute new matter. Withdrawal of the rejection is respectfully requested.

Conclusion

In light of the forgoing Amendment and Remarks, Applicants' assert the claims are in condition for allowance. Early notice of allowable claims is requested. The Examiner is invited to telephone the undersigned attorney for clarification of any of these Remarks or Amendments, or to otherwise speed prosecution of this case.

Respectfully submitted,

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Date: May 24, 2005

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